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THE IMPACT OF THE GUT MICROBIOME ON DEPRESSION AND ITS THERAPEUTIC INTERVENTION: A REVIEW

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ABSTRACT
Depression is one of the most prevalent mental illnesses and is often associated withVarious other medical disorders. Since the 1980s, the primary pharmacological treatment has been Antidepressants, but due to the recent discovery of the association between the gut microbiome andMental health, probiotics have been proposed as an adjunctive or alternate treatment. The human Gut microbiome partakes in a bi directional communication pathway with the central nervous System (CNS), named the microbiota–gut–brain axis. The micro biota–gut–brain axis is believed To modulate various central processes through the vagus nerve as well as production of microbial Metabolites and immune mediators which trigger changes in neurotransmission, neuro Inflammation, and behavior. Little is understood about the utilization of microbiome manipulationTo treat disease. In this narrative review, we aim to provide a holistic perspective by synthesizing And evaluating existing evidence, discussing key biological mechanisms, exploring the history of Probiotic use, and appreciating the influence of modern diet on mental health. Five online databases Were searched for relevant studies up to December 2017. Systematic reviews that included Randomized controlled trials assessing the efficacy of probiotics in the treatment of depressive Symptoms were included.

KEYWORDS: *Depression, Gut, Microbiome, Microbiota,*

INTRODUCTION
Depression is a common and serious neuropsychiatric disease affecting more than 300 million people of all ages across the globe. According to the World Health Organization, it is one of the leading causes of disability worldwide and a major contributor to the overall global disease burden The human gut microbiome, comprised of approximately 1800 different phyla and 40,000 bacterial species, has been implicated in numer ous aspects of human health and disease [1]. It partakes in a bidirectional communication pathway with the central nervous system (CNS), aptly named the microbiota–gut–brain axis. The microbiota–gut–brain axis is believed to modu late various central processes through the vagus nerve as well as production of microbial metabolites and immune mediators which trig ger changes in neurotransmission, neuro inflammation, and behavior [2–5]. Disruptions to the gut microbiome have been correlated with several neuropsychiatric disorders, including Parkinson's disease, autism, schizophrenia, and depression . The exact mechanism by which the gut microbiota causes or alters neuropsychiatric disease states is not fully understood. Further studies are required to elucidate the role of the microbiota–gut–brain axis, with the goal of preventing disease, identifying new therapeutic targets, and improving treatments. In this review, we focus on recent studies investigating the relationship between gut microbiome dysbiosis and the pathogenesis of depression[2]

Major Depressive Disorder (MDD) is a debilitating psychiatric illness affecting an estimated 300 million people worldwide (1). MDD is the leading cause of disability globally (2) and is associated with ~800,000 suicide deaths annually (3). Despite significant advances in our understanding of the etiology of MDD (4), existing knowledge is incomplete, treatments are inadequate, and new insights into MDD pathophysiology are urgently needed. One novel area of investigation related to MDD pathophysiology is the gut microbiome. The microbiome is a collection of trillions of microorganisms, including bacteria, that inhabit and interact with human hosts, with effects ranging from beneficial to pathogenic (5), and also more specifically refers to the collection of microbiota and their genetic material (6). Groups of bacteria are organized on a phylogenetic tree with taxonomical categories ranging from low resolution (kingdom, phylum) to high resolution (genus, species) taxa. The gut microbiota are considered so necessary and so integrated into host function that some describe this population as an overlooked organ (7). Beyond the breakdown of otherwise indigestible food substances and production of micronutrients, gut microbiota affect the hypothalamic- pituitary-adrenal axis (HPA) (8), produce neurologically active substances such as gamma-aminobutyric acid (GABA) (9) and short-chain fatty acids (SCFAs) (10), and influence the immune system and gut barrier (11–16). A growing body of literature supports and characterizes a gut-brain axis, and elucidates a possible role of gut microbiome dysfunction in major depression. Associations between the gut microbiome and depression have been identified in studies of inflammatory states and gut barrier health (17–19). In addition, animal studies have supported the possibility of a causative role of dysbiosis (disruption of the microbiome) in depression like behaviors. Broad-spectrum antibiotic administration in mice leads to

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dysbiosis, depression-like behavior, and altered neuronal hippocampal firing, with reversal of this phenotype following probiotic treatment with Lactobacillus casei DG (20). Male germ-free mice also exhibit elevated levels of serotonin (5 hydroxytryptamine) and its metabolite, 5-hydroxyindoleacetic acid in the hippocampus[1]

Anxiety and depressive disorders are ubiquitous and debilitating psychiatric conditions that collectively affect close to 10% of the global population every year (World Health Organization, 2017). The World Health Organization (2019) estimates the global loss in productivity due to anxiety and depressive disorders amounts to $1 trillion USD per year a trajectory expected to rise (Doran & Kinchin, 2019). Although engagement with psychotherapeutic and psychotropic treatments has increased over the past several decades (Olfson, Druss, & Marcus, 2015; Stephenson, Karanges, & McGregor, 2012), the prevalence and burden of anxiety and depressive disorders remains unchanged (Jorm, Patten, Brugha, & Mojtabai, 2017). Furthermore, there is substantial variation in response to existing treatments, which are overall efficacious in less than half of diagnosed patients (Casacalenda, Perry, & Looper, 2002; Cipriani et al., 2018). Accordingly, in order to develop more effective treatment targets, there is an urgent need to gain new insight into the underlying pathophysiology of anxiety and depressive disorders. The high comorbidity between internalizing disorders has been cited as evidence for possible shared physiological processes, risk factors, and illness trajectories (Kotov et al., 2017). One such promising area of research is the microbiota-gut-brain axis, which may elucidate shared pathophysiology. A growing body of research describes the bidirectional communication between the gut microbiota – the ecosystem of trillions of bacteria, viruses, archaea and fungi, along with their collective gene pool – with the host‟s central nervous system (CNS; Dinan & Cryan, 2015, 2017; Rieder, Wisniewski, Alderman, & Campbell, 2017). This biochemical signaling pathway, also known as the gut-brain-axis, is thought to influence cognitive functioning and mood via neural, metabolic, hormonal, and immune-mediated mechanisms (Foster & McVey Neufeld, 2013). The gut microbiota is a key regulator within the gut-brain-axis: bacterial species regulate the production of neurotransmitters and their precursors (e.g., serotonin, GABA, tryptophan), and can secrete and upregulate essential proteins and metabolites involved in neuropeptide and gut hormone release, such as short-chain fatty acids (SCFAs; e.g., Faecalibacterium prausnitzii and Clostridium leptum) and brain-derived neurotrophic factor (BDNF; e.g., Bifidobacterium; Bercik et al., 2010; O‟Sullivan et al., 2011; Parada Venegas et al., 2019). Furthermore, vagal and spinal afferent pathways mediate neural communication between gut microbes and the CNS, and the gut microbiota modulates immune signaling from gut to brain, via cytokine induction (Dinan & Cryan, 2017; Foster

The extant literature indicates that gut microbes may also be involved in the development and function of the hypothalamic-pituitary-adrenal (HPA) axis, which coordinates the adaptive stress response in the body (Foster et al., 2017; Sudo et al., 2004). Dysregulated HPA axis signaling is implicated in anxiety and depressive disorders, typically associated with higher levels of cortisol and inflammatory mediators that lead to a sustained proinflammatory state (Keller et al., 2017; Winter, Hart, Charlesworth, & Sharpley, 2018). Not only can the gut microbiota contribute to increases in cortisol and inflammation (Kamada, Seo, Chen, & Núñez, 2013), proinflammatory states may compound microbiota alterations via deleterious effects on gastrointestinal health. Excessive levels of circulating cortisol and inflammatory mediators increase intestinal permeability, thus allowing Gram negative bacteria to translocate into the bloodstream which may induce chronic CNS inflammation (i.e., bacteria which contain an additional lipopolysaccharide exterior membrane, associated with inflammation in high concentrations; Foster et al., 2017; T.-T. Huang et al., 2019). This suggests that microbiota-driven inflammatory responses may contribute to affective disorders, due in part to increased intestinal permeability. Similarly, gastrointestinal conditions suspected to involve alterations in the gut microbiota and intestinal permeability co-occur at remarkably high rates with psychiatric disorders (e.g., irritable bowel syndrome; Simpson, Mu, Haslam, Schwartz, & Simmons, 2020). Hence, the role of the gut microbiota in mood regulation and emotional processing, via the gut-brain-axis, may be of particular relevance to anxiety and depression etiology. Given the role of gastrointestinal bacteria in the bidirectional communication between the gut and the brain, recent studies have focused on characterizing gut microbiota composition in anxiety and depression. Preclinical models highlight gut microbiota disturbances in rodents exhibiting anxiety- and depressive- like behaviors, and report normalization of both behavioral and microbial alterations after bacterial probiotic administration (Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014; Mayer, Tillisch, & Gupta, 2015). Extension of this research into humans has been relatively slow prior to the last several years. Reviews have highlighted gut microbiota alterations in clinical depressive disorders relative to healthy control groups (Cheung et al., 2019; T.-T. Huang et al., 2019; Sanada et al., 2020); however, findings related to the diversity of microbial communities in depression are inconsistent, and it is unclear whether specific bacterial taxa drive group differences (Cheung et al., 2019; T.-T. Huang et al., 2019; Sanada et al., 2020). Existing reviews have also inadequately considered research quality and the effects of confounders, particularly diet and psychotropic medication (Simpson, Schwartz, & Simmons, 2020). The extant literature indicates that gut microbes may also be involved in the development and function of the hypothalamic-pituitary-adrenal (HPA) axis, which coordinates the adaptive stress response in the body (Foster et al., 2017; Sudo et al., 2004). Dysregulated HPA axis signaling is implicated in anxiety and depressive disorders, typically associated with higher levels of cortisol and inflammatory mediators that lead to a sustained proinflammatory state (Keller et al., 2017; Winter, Hart, Charlesworth, & Sharpley, 2018). Not only can the gut microbiota contribute to increases in cortisol and inflammation (Kamada, Seo, Chen, & Núñez, 2013), proinflammatory states may compound microbiota alterations via deleterious effects on

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Depression is one of the most prevalent mental illnesses worldwide and is the fourth leading cause of global disease burden in women.1 It is often associated with major medical illnesses, such as cardiovascu lar disease, diabetes, and cancer, adding to their morbidity.1–3 Medi cations were first used as treatments for depression in 1958, and the f irst antidepressant medication to be marketed as such, imipramine, was introduced in 1959.4 Since the 1980s, pharmacological treatment with antidepressant medications has been a major modality of thera peutic intervention in the management of depressive disorders.5 From 1987 to 1997, antidepressant usage among populations diagnosed with major depressive disorder (MDD) increased from 37% to 74%.5 However, a large portion of patients that have been prescribed antide pressants do not meet the DSM criteria for MDD, as antidepressants are commonly prescribed for anxiety disorders, obsessive–compulsive disorder, and sub-threshold depression, among other disorders. The ‘over- prescription’ of antidepressants has contributed to the common problem of polypharmacy.6 As a result, we are now seeing growing interest in non-pharmacological strategies for depression and other mental illnesses. An example of a non-pharmacological interven tion is physical exercise, which has been used as treatment for a variety of mental illnesses, including depression, and there are multiple system atic reviews of randomized controlled trials (RCT) that have demon strated its therapeutic effect.7 More recently, we have seen a growing focus in the literature on the role of gut bacteria on mental health. There has been much discussion in the literature surrounding the association between depression, irritable bowel syndrome, and inflammatory bowel disease. One study in Canada looked at the National Population Health Survey from 1996–1997 and found that the population diagnosed with inflammatory bowel disease had three fold the rate of depression as the general public.8 This association could be related to changes in the gut microbiome that result from the disease process.9 However, this correlation could also be explained by the general burden of disease, the rise in inflammatory markers in the blood, or corticosteroid treatment.10 In 2001, the World Health Organization published a report indi cating the health benefits of probiotic supplements, and in 2005, the f irst paper was published that proposed the use of probiotics as an adjunctive treatment for MDD.11,12 Since then, the field has steadily grown with a recent spike in publications. In fact, over 90% of the articles published on the microbiome in PubMed were from 2010 onwards.13 There has been particular focus on the effect of gut micro organisms on the brain through the gut–brain axis. In 2013, the term ‘psychobiotic’ was born due to both the growing evidence in the liter ature for the use of probiotic supplements for mental health and the resulting media attention.14 The evidence for the potential therapeutic benefits of probiotics for mental health was initially based on animal studies. One rat study found that Bifidobacteria infantis treatment significantly increased tryptophan, a serotonergic precursor, in the blood plasma ($P < 0.005$).15 It also decreased inflammatory markers, such as inter feron (IFN)-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-6. This finding is consistent with the inflammatory model of depression [6]

Literature Search for Gut Microbiome

Studies in MDD To identify putative depression-relevant aspects of gut microbiome composition, a PubMed literature search was performed that included articles published prior to February 28, 2018 with combinations of the terms “depression,” “depressive disorder,” “stool,” “fecal,” “gut,” and “microbiome.” Additional relevant articles were sought through manual bibliography search. Eligibility criteria were: (1) articles in English; (2) human case-control studies; (3) articles focused on depression; and (4) gut microbiota quantified from stool samples. Two raters (SGC and ARG) reviewed all search results and came to a consensus about inclusion/exclusion of each article.

Epidemiology

Depression is one of the most prevalent mental health disorders in the USA and the second leading cause of disability worldwide . A major depressive episode is defined as a depressed mood

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and/or loss of interest or plea sure in life activities for at least 2 weeks, with at least five symptoms that disrupt social interactions, work, or other important areas of daily life [. This may include symptoms such as unintentional weight change, insomnia or hypersomnia, agitation or psychomotor retar dation, fatigue, or feelings of worthlessness or guilt. In 2017, 17.3 million adults (6.8%) and 3.2 million adolescents (13.3%) in the USA experienced at least one major depressive epi sode . In addition to causing significant functional impairment, depression is also associated with substantial economic burden. From 2005 to 2010, the economic burden of individuals with major depressive disorders (MDD) in adults increased from $173.2 to $210.5 billion . Medical and pharmaceutical services directly related to the treatment of MDD accounted for $27.7 billion of the $210.5 billion total cost in 2010. The remaining costs were primarily those associated with comorbidities incurred by per sons with MDD, though suicide-related and workplace costs also contributed to the total economic burden. In light of these estimates, it evident that depression is a complex disorder that greatly impacts both individuals and soci ety. Implementation of preventative measures and effective interventions are required in order to address the challenges that depression presents.[2]

ANIMAL STUDIES

Gut Microbiota Depletion in Adult Rats

A notable finding in microbiome research is that greater species diversity among bacteria colonizing the gut appears protective against various ailments. To assess the effects of dis rupting a presumably healthy microbiome, Hoban et al. investigated the behavioral and neurochemical consequences of chronic gut microbiota depletion during adulthood within rats . A 6-week course of antibiotics was administered in drinking water to ten adult male rats in order to deplete intestinal micro biota, while ten adult male rats in the control group received autoclaved water devoid of any antibiotics. After the 6 weeks, all rats underwent testing to assess anxiety-like behaviors, depres sive-like behaviors, spatial learning, novel object recognition, somatic pain sensitivity, colorectal distention, brain monoamine levels, corticosterone levels, microbiota composition, and gene expression in the CNS The authors found that antibiotic treatment resulted in significant depressive-like behaviors (p\0.04), but demonstrated no impact on anxiety- like behaviors. Chronic antibiotic treatment was also associated with impaired spatial learning (p = 0.037) and lower visceral hypersensitivity (p = 0.015). Considering monoamines, rats treated with antibiotics exhibited a reduction in 5-hydroxytryptamine (5-HT) and an increase in 5-hydroxyin doleacetic acid (5-HIAA)/5-HT turnover in the hippocampus (p = 0.0004). Tryptophan levels also increased in antibiotic-treated rats (p = 0.032). Additionally, an increase in nora drenaline in the striatum (p\0.003) and increases in levodopa (L-DOPA) in the prefrontal cortex and hippocampus (p\0.0001) were noted. Dopamine precursor homovanillic acid (HVA) levels were also increased in the pre frontal cortex and hippocampus (p\0.05).

No significant difference was noted in plasma cor ticosterone levels in control versus antibiotic treated rats. Analysis of gene expression showed decreased levels of glucocorticoid receptor Nr3c1 (p\0.05) and corticotrophin- releasing hormone receptor 1 (p\0.01) in the hip pocampus and amygdala of antibiotic-treated rats, while Bdnf levels were increased in the amygdala (p\0.01). Decreased levels of Crch1 were also noted in the hippocampus and amygdala (p\0.01). Lastly, rats treated with antibiotics exhibited altered microbial diversity, with a significant decrease in Firmicutes and Bacteroidetes and an increase in Proteobacteria and Cyanobacteria. From these findings, the authors were able to identify a distinct phenotype, which included depressive-like behaviors and impaired cogni tion, that was associated with antibiotic-in duced microbiota depletion in rats during adulthood. Furthermore, the study corrobo rated existing literature on the importance of the gut microbiota on tryptophan availability and the CNS serotonergic system. Chronic antibiotic exposure decreased the diversity and richness of the gut microbiota, coinciding with the display of depressive-like behavior. Decreased levels of hippocampal 5-HT and 5-HT/5HIAA turnover and altered levels of L DOPA and HVA reflected a dysregulation of monoamine synthesis and degradation, indi cating that dysbiosis may profoundly impact neurotransmitter systems.[2]

HUMAN STUDIES

Altered Fecal Microbiota in Major Depressive Disorders

Jiang et al. analyzed fecal microbiota composi tions in active MDD (A-MDD), responding MDD (R-MDD), and healthy controls (HC) to determine alterations in active episodes of MDD and possible dysbiosis in response to antide pressant treatment . Forty-six patients were recruited and screened by one psychiatrist with the Mini- International Neuropsychiatric Inter view for pre-existing psychiatric conditions, and the presence of MDD was verified using the Structured Clinical Interview for the Diagnosis and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV). Severity of disease was determined with Hamilton Depression Rating Scale (HAM-D) and Montgomery-Asberg Depression Rating Scale (MADRS). Severity scores were used to separate A-MDD (HAM-D score C 20) and R-MDD (baseline HAM-D score C 20). On the basis of the results of examination, subjects were divided into an A-MDD group (n = 29) and R-MDD group (n = 17). HC (n = 30) subjects were also selected from the same cohort. Fecal and serum samples were collected when HAM-Dscores were reduced by 50% post treatment. Surprisingly, analysis of bacterial diversity and richness showed significant increases in bacterial diversity in A-MDD rela tive to HC as evaluated by the Shannon Index. While it is conventionally considered beneficial to have greater gut microbiome diversity, this diversity is untested in regards to its effects on CNS functions, and may not be universally beneficial. The authors cite studies by Fan et al. and Roger et al. which show increases in microbiome diversity in CNS altered popula tions such as autism, alluding to a potentially negative impact of increased microbiome diversity [39, 40]. Serum samples were evaluated for inflam matory biomarkers TNFa, IL-1b, IL-6, and BDNF, as inflammation has been associated with dys biosis and MDD. Notably, serum analysis showed no significant differences

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between A-MDD, H-MDD, and HC subjects with regards to IL-6, TNFa, and IL-1b. BDNF levels were lower in A-MDDandR-MDDcomparedtoHC.Further studies are needed to determine causation, to better elucidate the role of the gut microbiome in CNS disorders such as MDD.[2]

Probiotic vs Prebiotic vs Placebo in Major Depressive Disorders: Akkasheh et al. analyzed the effects of probiotic intake on symptoms of depression and meta bolic status in patients with MDD [49]. They conducted a randomized, double blind, pla cebo-controlled trial of 40 patients with MDD (DSM-IV criteria). Patients were randomly assigned to either a probiotic (n = 20) or placebo group (n = 20). Probiotic supplementation con sisted of combination of Lactobacillus aci dophilus, Lactobacillus casei, and Bifidobacterium bifidum. In the probiotic group, significantly reduced BDI scores were observed compared to placebo, along with a significant decrease in anxiety symptoms. The authors hypothesized that increased levels of tryptophan lead to decreased serotonin metabolite concentrations in the frontal cortex and decreased dopamine levels in the amygdaloid cortex. Probiotics, through fer mentation of dietary components, may be able to change the composition or activity of the normal gut flora. This may result in improved peripheral and central nervous system symp toms. Probiotics may also directly influence the enteric and central nervous systems in addition to their mucosal immune system effects. Decreased serum insulin concentrations and HOMA-IR (homeostatic model assessment of insulin resistance) were also observed in the probiotic group. No significant changes were noted for FPG (fasting plasma glucose), HOMA B (homeostatic model assessment for beta cells), QUICKI (quantitative insulin-sensitivity check index), or lipid profiles. The literature supports no changes in lipid profile, though the decrease in insulin levels observed in the probiotic group is a unique finding. Insulin reduction may be due to increased hepatic natural killer T cell numbers and a reduction in inflammatory sig naling. Linoleic acid is also produced by some species of Lactobacillus, which may upregulate adiponectin and downregulate inflammation to block suppression of GLUT4 transporters. High sensitivity C-reactive protein (hs-CRP) was also decreased in the probiotic group. Hs CRP is a marker of systemic inflammation and a predictor of adverse cardiovascular events. The anti-inflammatory effects of probiotics may be due to production of SCFAs in the colon and decreased expression of IL-6. An increase in plasma reduced glutathione (GSH) was also observed in the probiotic group. However, no changes on total antioxidant capacity levels were seen. Although the mechanism of oxida tive stress is unknown, the beneficial effects of probiotics on GSH levels might be due to enhanced glutamate–cysteine ligase activity, thereby increasing synthesis of GSH.[2]

Mechanisms Through Which the Microbiota may be Associated With Psychopathology.

Like the six articles reviewed here, many studies of the microbiome have focused on the relative abundance of specific microbial operational taxonomic units (OTUs) and health outcomes of interest. However, looking for specific taxa as a marker of disease may miss important information for certain conditions. Although a great number of microbial taxa are found in the human gut microbiome, a limited number will take up niches in any one individual. For example, over 1,000 bacterial species were identified in a sample of 124 subjects. Each individual's feces harbored at least 160 species, but much of the bacterial DNA coded for similar processes (41). Gut microbiome distribution across individuals demonstrates surprisingly low convergence even between individuals on identical diets , in accord with evidence of conserved metabolic processes across taxa . This suggests that different individuals can have taxonomically varied but functionally similar microbiota, i.e., the same or similar essential functions can be performed by a variety of microbial taxa. Likewise, varied permutations of microbial communities can take up nutritional and locational niches depending on opportunity and environment . With respect to exploration of the gut microbiome's effects on depression, understanding microbial functions may therefore be more illuminating than focusing on relative abundance of specific taxa. Chen et al. (30), the most recent of the reviewed articles, attempted to address this by employing a proteomic analysis method to produce comparative functional assessment based on the identified bacterial proteins. The impact of this article is necessarily limited by the problem of generalizing from a very small sample size (n = 10 MDD/10 controls). Fundamental bacterial functions involve consumption of substrates and production of metabolites (44). A taxon's specific pattern of substrate and nutrient usage may shed light on its survival fitness in certain environments and its ability to use available materials for products, some of which may be relevant to depression. Bacteria often demonstrate symbiotic relationships with other taxa, metabolizing substrates into products which maybenefit themselves, feed or otherwise benefit their neighbors and host, or influence/signal their neighbors and host . Of particular interest with respect to depression etiology are products that can interact with the nervous systems (central and enteral) or play a role in immune responses such as inflammation. Gut microbiota benefit the host in multiple ways, include digesting/fermenting carbohydrates, producing micronutrients, mounting immune responses to discourage colonization by pathogens, and producing a variety of neuroactive molecules Thus, multiple possible pathways exist whereby the microbiome may either contribute to or confer resilience against depression. Some instances are explored below.[1]

Bacterial Metabolism of Carbohydrates and Proteins

Dietary carbohydrates, including indigestible oligosaccharides, are a common substrate for gut bacteria, which transform them into short chain fatty acids (SCFAs), including acetate, propionate, butyrate, and valerate. These substances serve as energy sources for the host and for other bacterial species . SCFAs also trigger differentiation of T cells (and can function as histone deacetylase inhibitors, which as a class have immunosuppressive and anti inflammatory functions and have been proposed as potential novel antidepressants Additionally SCFAs activate G protein-coupled receptors , are involved in neurotransmitter production

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and neuroprotection, and can themselves penetrate the blood-brain barrier We looked broadly at reports of SCFA production among the reviewed case-control studies and found that in general the genera reduced in MDD have extensive capacity to metabolize carbohydrates, particularly mono- and disaccharides and their derivatives [Bifidobacterium , Faecalibacterium , and Ruminococcus . Bacteroides, found to be reduced in a treatment-nonresponsive depressed subgroup compared to healthy controls , as a genus has a particularly rich armamentarium for metabolizing more complex carbohydrates including glycans of human mucin . In contrast, although reported as elevated in MDD also can metabolize carbohydrates [Anaerostipemay be noteworthy that several are high metabolizers of amino acids and proteins [Clostridium , Klebsiella , Parabacteroides, Streptococcus Oscillibacter and Alistipes . Increased metabolism of proteins by microbiota involves fermentation, or bacterial putrefaction, a process that may divert essential host amino acids from the host to the microbes and may result in toxic products such as ammonia, putrescine, and phenol . Dysbiosis that results in increased putrefaction has been implicated in the pathogenesis of colorectal cancer and autism spectrum disorders . With regard to depression, in a large epidemiologic study, elevated dietary intake of protein at baseline was associated with more severe depressive symptoms at 10-year follow-up in a dose-dependent manner, in women only Others have reported that interactions between dietary protein levels and genetic polymorphisms can moderate the risk of depression . Thus, while not quantitatively testable across the studies reviewed here, we may speculate that dysbiosis resulting in a relatively lower capacity to metabolize carbohydrates and higher capacity for protein metabolism may have a role in the pathogenesis of MDD. Lower SCFA could contribute to symptomatology as a result of lower energy and altered neurotransmission, while both lower SCFA and higher putrefaction products are implicated in intestinal inflammation, relevant here as inflammatory bowel conditions have been associated with a high co-morbidity with depression and anxiety . We have focused our discussion on mechanisms through which dysbiosis could contribute to the development of depression. However, the directionality of the associations between inflammatory bowel disease and depression is not known. Thus, it is also plausible that depression may cause digestive problems and dysbiosis either through altered dietary choices or other mechanisms. One hypothesis could be that in some individuals, depression confers a decreased ability to digest proteins; the resulting increased residual protein in the colon would give an advantage to higher concentrations of microbes which prefer proteins as substrates, leading to higher putrefaction and inflammation.[1]

Production of Micronutrients

Water-soluble vitamins from the diet may be absorbed from the small intestine, including ascorbate (vitamin C), biotin (B7), folate (B9), niacin (B3), pantothenic acid (B5) pyridoxine (B6), riboflavin (B2), and thiamine (B1) . However, a number of these water-soluble vitamins also can be generated by microbiota and absorbed in the colon and thereby affect the host . Therefore, dysbiosis resulting in low production of micronutrients could contribute to depression pathophysiology, particularly in the case of depressed patients with poor nutritional intake. For example, Bifidobacterium, among the genera that were less abundant in MDD in reviewed case-control studies, can synthesize riboflavin, niacin, and folate . Low folate levels have been associated with the presence of depression by meta-analysis, and folate levels were inversely associated with depressive symptom severity in one epidemiological study . The relative contribution of dietary vs. bacterial folate to the host is not clear ; however, a carrier for uptake of folate into human colonocytes has been described in cell culture and ex vivo studies. Deficiency of thiamine is implicated in depressive symptoms in older adults Microbial production results in a pool of free, absorbable thiamine and, similarly to folate, specific carrier proteins exist to transport free thiamine into both intestinal enterocytes and colonocytes . Microbial production of vitamins also may affect humans indirectly in a kind of food chain where vitamins produced by certain microbes are needed by other microbiota whose downstream products impact depression. For example, about half of human gut microbes are thiamine auxotrophs, i.e., they require but cannot make their own thiamine [1]

Inflammatory Regulation Depression and anxiety

Symptoms increase with functional gut disorders . Irritable bowel syndrome (IBS) has been characterized by increased permeability of the mucosal layer as well as gut microbiome dysbiosis . Inflammation can compromise normal barriers protecting the body from pathogenic gut bacteria , resulting in intestinal permeability , or “leaky gut,” and even leakage at the blood-brain barrier . One mechanism whereby this occurs is tumor necrosis factor alpha (TNFα) induction of shedding and apopotosis of intestinal epithelial cells . This has been suggested as an explanation for the high association of inflammatory gastrointestinal disorders with depression; for example, 49% of people with inflammatory bowel disease suffer from depressive symptoms. Gut dysbiosis promotion of inflammation may contribute to multiple pathways in the CNS that are implicated in the development of depression. Upregulation of inflammatory cytokines has downstream consequences in brain, including shunting of tryptophan away from serotonin synthesis toward the kynurenine pathway as well as excitotoxic and neurotoxic effects[1]

Production of Neurotransmitters

In cell culture studies, gut microbiota have been found to make precursers to neurotransmitters, such as tryptamine and neurotransmitters including GABA serotonin, norepinephrine, and dopamine , Among the bacteria found in the reviewed studies to be lower in MDD(28), Bifidobacterium is an efficient producer of GABA . Several bacterial strains are known to produce serotonin directly . Moreover, one study reported that male rodents reared in a germ-free environment, a profound manipulation of the microbiome, exhibit increased levels of serotonin in the hippocampus, along with increased peripheral levels of tryptophan, a serotonin precursor, suggesting the

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possibility of a peripheral origin to this effect . Another animal study found that administration of a probiotic containing Lactobacillus plantarum PS128 led to both antidepressant-like effects in mice as well as increases in levels of serotonin and dopamine in the striatum . Modulation of neurotransmitter production is one possible means by which the gut microbiome may affect the brain, with direct relevance to depression.[1]

Human Brain Imaging Supporting Gut Microbiome-Brain Communication

The current literature supports bidirectional interactions between the gut and brain mediated by gut microbiota . There is evidence that gut microbiome composition is correlated with neural activity and brain structure in humans, as assessed by functional and structural MRI . Specificially, an observational study in obese and non-obese individuals found that both microbial diversity as well as relative abundance of Actinobacteria were associated with measures of white matter integrity and of regional iron content in the brain Another study in healthy female volunteers identified two clusters of individuals based on bacterial genotyping, a Bacteroides-abundant group and a Prevotella- abundant group, and observed differences in measures of both structural and functional neuroimaging when comparing these groups . Both Bacteroides and Prevotella were associated with MDD in specific case-control studies and exhibited divergent directionality. Moreover, probiotic interventions can alter neural responses assessed by fMRI . Specifically, randomized, double blind, placebo-controlled treatment with Bifidobacterium longum in patients with irritable bowel syndrome led to reduction in neural responses to emotionally negative stimuli in limbic brain regions including the amygdala. Likewise, B. longum administration to mice via oral gavage had an anxiolytic effect, and this was not seen in vagotomized animals [1] .

Another small randomized trial in healthy women found that administration of a probiotic containing multiple species was associated with a decrease in neural responses to an emotional faces attention task in a broad network of brain regions, including insula and somatosensory processing regions . In rodents, oral gavage administration of Lactobacillus rhamnosus, which improved anxiety- and depression-like behaviors, also caused brain region-specific alterations in GABAAα2 mRNA expression detected by in situ hybridization . Neither the neurochemical nor the behavioral effects were seen in vagotomized animals, indicating that the vagus nerve mediated this particular communication between the gut microbiota and brain. Important features of gut-brain communication that require further elucidation with respect to influences in MDDincludethe different roles of luminal vs. systemic bacteria, the mechanisms of traversing the gut barrier into the portal circulation and the blood-brain barrier (BBB), and the role of the vagus nerve.[1]

Modern living and the rise of depression

Depression has arguably been on the rise since the early 20th cen tury.67 There are many factors that can account for this change that range from political to philosophical, for instance, the two World Wars and rise of totalitarian regimes, along with the increased sense of individual nihilism that pervaded the Western social conscience as a consequence of modernist and postmodernist thinkers.5 Anewer contribution to the explanation may be related to the role of the microbiome in the gut–brain axis. The nature, variety, and density of bacterial species in the gut could have been affected by significant changes in the food industry that occurred in the 20th century, as well as an increased use of antibiotics and an increase in overall hygiene. Based on comparisons with the Hadza of Tanzania, a hunter– gatherer tribe that is unaffected by these social changes, the civilized human being has markedly decreased diversity in gut microbiota.57 Micro biota diversity is essential in providing the microbiome with the abil ity to adapt to changes in the environment.57 A lack of diversity renders the gut susceptible to diseases and alteration based on envi ronmental changes. We believe it is possible that changes in our gut microbiome that may have resulted from hyper-sanitation and modern dietary styles have contributed to the rise in depression throughout the decades, despite an overall improvement in the quality of living.57 Studies that explore the impact of dietary and lifestyle changes on the microbiome and, by direct or indirect extension, mental health in gen eral and depression in particular, are needed and may have major pub lic health implications.[6]

Role of diet

Dietary effects on the gut microbiome are evident as early as infancy, with gut microbiome differences observed between breast-fed and formula-fed infants, including a greater prevalence of Bifidobacteria in breast-fed infants . In adulthood, gut microbiome composition is associated with self reported long-term dietary patterns, with a higher prevalence of Prevotella observed in individuals reporting higher intake of carbohydrates and simple sugars, and a higher prevalence of Bacteroides observed in individuals reporting higher intake of animal protein and saturated fats. Effects of short term dietary interventions on the gut microbiome are not well understood. As one example, probiotic administration in a recent study led not only to changes in brain activity assessed by fMRI (see section Human Brain Imaging Supporting Gut Microbiome-Brain Communication above), but also to antidepressant effects and changes in urine metabolic profiles, suggestive of microbiome effects, but no measureable effects on gut microbiome composition were detected by fecal 16S rRNA gene sequencing . It is unclear to what extent this finding reflects limitations in our current microbiome quantification tools, or resistance of the gut microbiome to change. One dietary factor in the microbiome-inflammation depression relationship is the intake of polyunsaturated fatty acids (PUFAs), especially with regard to the ratio of omega-3 to omega-6 PUFAs, which has been found to be low in depression. Omega-3 PUFAs tend to be anti-inflammatory while omega-6 PUFAs such as arachidonic acid tend to be pro inflammatory [reviewed in], and the PUFA balance has effects on mucus adhesion of bacteria . For example, in a study of gnotobiotic piglets the growth and mucus adhesion of probiotic Lactobacillus paracasei were enhanced by concomitant administration of a

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mixture of PUFAs (126). Omega-6 PUFAs also are implicated in epithelial permeability and mucosal damage through the generation of leukotrienes, inflammatory metabolites of arachidonic acid . Dietary PUFA serves as a substrate for some gut microbes, and PUFA-derived metabolites have been proposed as novel gut microbial products that may have important physiological effects (16, 128). Among the genera reported in the reviewed case- control studies as less abundant in MDD, Bifidobacterium degrades unsaturated fatty acids including linoleic acid , a precursor to arachidonic acid

Clinical and Metabolic Responses to Probiotics in Major Depressive Disorders

Kazemi et al. conducted a randomized, double blind, placebo-controlled study to compare the effects of probiotic and prebiotic supplementa tion on the BDI as a primary outcome, and the kynurenine/tryptophan ratio and tryptophan/ branched chain amino acids (BCAAs) ratio as secondary outcomes in patients with MDD . Atotal of 81 patients were enrolled in this study and randomly assigned to probiotic group (n = 28), prebiotic group (n = 27), and placebo group (n = 26). The bacteria used in the probi otic group consisted of Lactobacillus helveticus and Bifidobacterium longum; the prebiotic was galacto-oligosaccharide. After 8 weeks of treatment, the probiotic group demonstrated a significant decrease in BDI score compared to both prebiotic and pla cebo groups ($p = 0.042$). These results were consistent with the literature, though this study is unique in that the use of probiotics was a primary method of treatment. The main mechanisms postulated for the observed probi otic BDI score reduction include modulation of neurotransmitters and inflammation. Additionally, serum kynurenine/tryptophan ratio was significantly reduced in the probiotic group compared to the placebo group ($p = 0.048$). The prebiotic group did not show any significant changes[2]

However, this result was only seen when adjusted for serum iso leucine. Tryptophan is metabolized by two main pathways, the serotonin and kynurenine pathways. Shunting of tryptophan towards the production of kynurenine leads to a serotonin deficiency. Probiotics, however, drive trypto phan metabolism down the serotonin pathway. This increase in serotonin may therefore reduce depression and anxiety by increasing the avail ability of serotonin, much like the mechanism behind SSRIs. Nosignificant increase in tryptophan/BCAAs ratio was observed in the probiotic group. However, the prebiotic group did show a sig nificant increase in the ratio when compared to the placebo group ($p = 0.031$). The authors theorize that the significance of this ratio is that BCAAs compete with tryptophan for passage through the blood–brain barrier. BCAAs are produced by some strains of gut bacteria. Notably, probiotics or prebiotics may reduce relative proportions of BCAA, thereby increas ing tryptophan entry to the brain and subse quent serotonin production. This could then theoretically decrease symptoms of depression and anxiety. Despite the fact that probiotics were shown to reduce depression in this study, they did not significantly alter the tryptophan/ BCAA ratio. Conversely, while prebiotics were able to increase the ratio of these components, prebiotics were not associated with a significant change in depressive symptoms. Though lim ited in size and scope, the study offers promise in the study of microbiome alterations in treating depression moving forward.[2]

Therapeutic approaches to gut microbiome

The novel research implies that the gut microbiota plays a critical role in the progression of cardiovascular illnesses. Therapeutic techniques for influencing the composition and metabolic activity of the gut microbiota have been developed. As showninFigure6,theseoptionsincludedietarychanges,theuseof probiotics and prebiotics, antibiotic treatments, and even fecal transplantation. Notably, these therapies have show n the potential to improve blood pressure control, restore lipid profiles to normal levels, andr educe body weight in people ewith cardio vascular disease

Dietary Inventions

Numerous scientific studies have provided persuasive eevidence supporting the idea that dietary interventions can significantly decrease the risk of cardiovascular problems(197,198).Dietsthat frequently occur in Western industrialized societies that feature high consumption of red meator animal proteins, saturatedfats, and simple carbohydrate s have been associated with an increased risk of CVD(199,200).An increasing mass of evidence refers to the intestinal microbiota as a possible avenue for CVD treatment. Current clinical trial sonmicrobe targeting for CVD therapy are

Limitations

Our review of this literature is limited to a descriptive approach. Because these studies were disparate in their aims andmethodologies, studied heterogeneous populations, reported on relative rather than absolute abundance, and were small and likely underpowered, a meta-analytic approach would be handicapped.

CONCLUSION

No consensus has emerged from existing human studies of depression and gut microbiome concerning which bacterial taxa are most relevant to depression This may in part be due to differences in study design. Given that bacterial functions are conserved across taxonomic groups, we propose that studying microbial functioning may be more productive than a purely taxonomic approach to understanding the gut microbiome in depression. The utilization of microbiome alterations to treat disease remains in its infancy. Though studies exploring its role in various disease processes generally show promise, mechanisms remain unclear and evidence-based treatments for most illnesses have not yet been developed

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